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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,672	12/09/2003	Shulamit Levenberg	0492611-0530/MIT-10077	6356

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
07/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@choate.com

Office Action Summary	Application No.	Applicant(s)	
	10/731,672	LEVENBERG ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50 and 59-77* is/are pending in the application.

4a) Of the above claim(s) *59-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-11,13-19,22-25,27-34,36-44,47-50,71 and 73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/1/09 has been entered.

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 59-77, 73 are pending. Claims 6, 12, 20-21, 26, 35, 45-46, 51-58, 72 and 74 are canceled. Claims 59-70 are withdrawn. Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71 and 73 are under consideration.

Applicant's election of the growth factor is maintained in view of the species election filed on 7/24/06.

DECLARATION UNDER 37 C.F.R. & 1.132

The declaration under 37 C.F.R. & 1.132 of Robert Langer has been considered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims **1-5, 7-11, 13-19, 22** rejection under 35 U.S.C. 102(a) as being anticipated by **Levenberg et al,** (PNAS, 99(7): 4391-4396, 2002) is withdrawn. In view of the declaration by Robert Langer the Levenberg et al cited reference is not anticipatory material.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, rejection under 35 U.S.C. 103(a) as being unpatentable over Levenberg in view of Benvenisty is withdrawn.

Claims 1-5, 7-11, 13-19, 22-25, 27-34, 36-44, 47-50, 71 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Wobus et al,** (J Mol Cell Cardiol, 29: 1525-1539, 1997); in view of **Itskovitz-Eldor et al** (Molecular Medicine, 6(2): 88-95, 2000); matrix **Badylak** (US 2003/0216812); **Mooney et al,** (Biomaterials, 17: 115-124, 1996); **Schuldiner et al** [PNAS, 97(21): 1107-11312, 2000 (IDS)].

Wobus et al, discloses the growth factor retinoic acid accelerates mouse embryonic stem cell-derived cardiac differentiation and enhances development of ventricular cardiomyocytes (title). Wobus teaches that treatment of embryonic stem cells (ES) cell-derived embryoid bodies with retinoic acid accelerated the differentiation of ES cells into cardiomyocytes, enhanced at the level of a-cardiac MHC and MLC-2v mRNA at an early developmental stage and resulted in an increased number of b-galactosidae-positive ventricular cardiomyocytes (p1526, 2nd column, 3rd paragraph) (claims1, 2, 13). Wobus teaches the embryonic cells co-cultivated on the adhesion promoter gelatin (0,1%) (p 1526, 2nd column, last paragraph) (Claim 13). Wobus teaches the embryoid bodies contained beating cardiomyocytes

(p 1527, 1st column last paragraph). Wobus differs from the present invention for not teaching human ES cells.

However, at the time of the instant invention **Itskovitz-Eldor et al** (Molecular Medicine, 6(2): 88-95, 2000) teaches human embryonic stem cells differentiate into cystic embryoid bodies (EBs) in a similar manner and time scale to those reported for mouse ES cells, where cardiac muscle differentiation depicted in pulsing EBs (p 93, 1st column, and figure 4). **Itskovitz-Eldor** suggests the in vitro differentiation of human ES cells into specific lineages can serve as a source of mature cells, which may be used in cell transplantation and offer an opportunity to study in vitro processes involved inhuman early embryogenesis (p 93, 2nd column last paragraph). Regarding the limitation of forming 3-D matrix **Badylak** (US 2003/0216812) teaches a tissue graft construct that comprises a matrix on which cardiac muscle cells, multi-potential progenitor cells (Abstract, p.2, paragraphs 0014) for use in repairing a diseased or damaged tissue (p.1, co1.2). Bodylak further teaches that endothelial cells used in the construct can be derived from any type of endothelial cells including arterial, venous or derived from progenitor cells or stem cells (p.2, co1.2 paragraph 0018). Badylak discloses various matrices that can be used to make said construct including APPLIGRAFR (Novartis) that is composed of a synthetic polylactic acid-containing composition (paragraph 0017, lines 13-15). Badylak clearly teaches in a embodiment (paragraph 0023) that the tissue graft construct shows surprisingly enhanced vascularization in vitro" and further in another embodiment (example see paragraph 0025 and 0037) teaches seeded endothelial cells are cultured in vitro for sufficient time to induce the formation of vessels or vessel like structures before implantation of the construct into the affected region. Badylak however, does not teach a 3-D cell support polymer matrix however, **Mooney et al,** (Biomaterials, 17: 115-124, 1996) teaches a 3D-polymer matrix made of poly(L-lactic acid) and poly(lactic acid-co-glycolic acid) (PLLA/PLGA) (entire article; abstract;

p.115, co1.2 bridging p.118) articlep.2, co1.2, paragraph 0016; p.4, co1.1) polymer scaffolds into which endothelial cells that are vasculogenic and smooth muscle cells were incorporated (p.119, co1.2) and in vitro condition to form tubes and with smooth muscle cell, the organization was similar to that is observed in blood vessels lp.119, co1.2). Money teaches Polyglycolic acid (PGA) fibre meshes are attractive candidates to transplant cells, but they are incapable of resisting significant compressional forces (abstract). To stabilize PGA meshes, atomized solutions of poly(L-lactic acid) (PLLA) and a 5060 copolymer of poly(o,L-lactic-co-glycolic acid) (PLGA) dissolved in chloroform were sprayed over meshes formed into hollow tubes (abstract). The PLLA and PLGA coated the

PGA fibres and physically bonded adjacent fibres. The pattern and extent of bonding was controlled by the concentration of polymer in the atomized solution and the total mass of polymer sprayed on the device. The compression resistance of devices increased with the extent of bonding, and PLLA bonded tubes resisted larger compressive forces than PLGA bonded tubes. Tubes bonded with PLLA degraded more slowly than devices bonded with PLGA. Implantation of PLLA bonded tubes into rats revealed that the devices maintained their structure during fibrovascular tissue ingrowth, resulting in the formation of a tubular structure with a central lumen. The potential of these devices to engineer specific tissues was exhibited by the finding that smooth muscle cells and endothelial cells seeded onto devices in *vitro* formed a tubular tissue with appropriate cell distribution (abstract). Regarding adding more biomolecules **Schuldiner et al** (PNAS, 97(21): 1107-11312, 2000) teaches that retinoic acid, EGF, BMP4 and basic FGF direct differentiation of human Es cells into cardiac cells (abstract). **Schuldiner et al** suggest those growth factors can be applied to determine whether the growth factors would affect human ES cell receptors (p 11310, 2nd column).

Thus it would have been obvious for one of ordinary skill in the art to replace the mouse ES cells of Wobus with human ES cells of Itskovitz-Eldor in the Bodylak's complex 3D-matrix comprising a polymer designed for culturing smooth muscle cells along with vascularizing endothelial cells in a 3D-matrix consisting essentially of polymers PLLA/PLGA to seed endothelial cells and smooth muscle cells in vitro to generate a vascularized muscle construct as taught by Mooney with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make a switch from mouse to human ES and use a matrix essentially made of polymers PLLA and PLGA in order to optimize the potential to engineer specific tissues since it was exhibited by the finding that smooth muscle cells and endothelial cells seeded onto devices in *vitro* formed a tubular tissue with appropriate cell distribution as taught by Badylak/Mooney and furthermore to determine whether the growth factors would affect human ES cell receptors as taught by Schuldiner. Other limitations of the claims that recite varying percentage of the cross-sectional area of the matrix is not reduced by contractile force exerted by the ES cells are implicit characteristics of the ES cells and one of ordinary skill in the art could have used the construct and the method of making the construct taught by the combined references to optimize the population of human embryonic cells comprising the matrix by adjusting growth factors and matrix components. One who would practice the invention would have had reasonable expectation of success because Itskovitz-Eldor embraced the potential of culturing hES cells in a similar fashion to mouse ES cells while Badylak/Mooney provided guidance with respect to 3-D vascular network like structure on matrix. Thus, it would have been routine modification for one of ordinary skill in art to select human embryonic for the construct for transplantation therapy. Applicants should note that the KSR case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. KSR International Co. v. Teleflex Inc., 550 U.S.-, 82USPQ2d 1385 (2007).

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Thus, the claimed invention as a whole is clearly prima facie obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "substantially free" in claim 72 is a relative term which renders the claim indefinite is withdrawn in view of the amendment.

The term "substantially free" in claim 74 is a relative term which renders the claim indefinite is withdrawn in view of the amendment.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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/Anne-Marie Falk/
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